REMARKS

A. Status of claims and specification

Claims 13, 14 and 33 are pending.

Claim 13 has been amended to recite that administration is parenterally, as supported at least at page 23, second full paragraph. Claim 13 has also been amended to recite that the inhibitor is the complete human type antibody, as supported at least at page 12, second full paragraph. Finally, claim 13 has been amended to recite that the cancer is cancer in which PD-L1 and PD-L2 is over-expressed, as supported at least at page 20, second full paragraph.

New claim 33 is supported at least at page 20, second full paragraph.

B. Title

The Examiner requires a new title that this descriptive of the claimed subject matter.

The current title has been replaced with the following title:

A Method for Treatment of Cancer by Inhibiting the Immunosuppressive Signal Induced by PD-1.

C. Abstract

The Examiner requires a new abstract that is limited to a single paragraph.

The current abstract has been re-formatted as one paragraph.

D. Claim Rejections - Under 35 USC 112, Second Paragraph

Claims 12-14 and 16 are rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

1. The Examiner asserts that claims 12 -14 and 16 are indefinite in the recitation of "immunosuppressive signal inhibitor of PD-1," because it is unclear whether the phrase means an inhibitor of the immunosuppressive signal of PD-1, or an inhibitor a PD-1 signal, which inhibitor is immunosuppressive.

For examination purposes, the Examiner has used the former correct interpretation.

This rejection is overcome by amending the claims to recite that the inhibitor is a completely human PD-1 antibody.

2. The Examiner asserts that claim 12 is indefinite in the recitation of a method, because the claim does not clearly set forth a preamble which indicates the purpose or endpoint of the method steps.

Claim 12 has been canceled, thus making this rejection moot.

E. Claim Rejections - Under 35 U.S.C. § 112, First Paragraph

1. Enablement

Claims 12-14 and 16 are rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the specification does not provide a sufficient enabling description of a method for immonopotentiation in vivo, or a method for treatment of cancer.

In particular, the Examiner asserts that the in vitro experiments and even the animal model studies historically have not correlated well with in vivo clinical trial results in patients. As a result, the Examiner asserts that clinical trials are needed to prove the efficacy of the treatment.

In support of this position, the Examiner maintains that the efficacy of therapeutic antibodies can be species- and model-dependent, and, therefore, it is unpredictable whether reliance on the experimental observations in the experimental model described in the instant specification provide the basis for employing the claimed antibodies for immunopotentiation in vivo, or for treating cancer. As evidence, the Examiner cites Blazar et al. (J. Immunol., 1996, 157: 3250 -3259; see entire document, in particular, e.g. page 3257, column 2, first paragraph) as disclosing that issues such as tissue distribution, half-life, affinity and avidity obtained with various reagents targeting co-stimulatory molecules might prove to be highly important in achieving a therapeutic effect. Therefore, according to the Examiner, any conclusion regarding the efficacy of co-stimulatory modulation on altering in vivo immune response should be interpreted in light of the specific reagent used (Blazar et al., see page 3257, column 2, forst paragraph).

In addition, the Examiner asserts that pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect; (2) the protein may not reach the target; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use.

Accordingly, the Examiner concludes that undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and

detailed description in Applicant's specification of the clinical protocols, and absent working examples providing evidence that the claimed methods are effective for immunopotentiation in vivo or for treating cancer.

For the following reasons, this rejection is traversed and/or overcome.

The Examiner has asserted that clinical trials are needed to prove the efficacy of the treatment of the present invention quoting Blazar et al. However, the Examiner is believed to have misinterpreted or misrepresented Blazar et al. Blazar et al. states on page 3257, column 2 first paragraph that there are issues such as tissue distribution, half-life affinity, and avidity that cause the differences in efficacy between CTLA4Ig and a combination of anti-CD80 and anti-CD86 mAb in achieving GVHD protection. However, Blazar et al. does not state that issues regarding a difference in efficacy exist between actual therapy and experiment.

Additionally, the Examiner has pointed to reasons (1) to (3) as support for the position that pharmaceutical therapies in the absence of in vivo clinical data are unpredictable. However, the claims have been amended to recite that the inhibitor is a completely human antibody and to recite parenteral administration. Completely humanized antibodies generally have low antigenicity in humans. Thus, they would not be inactivated before producing an effect and would have few controversial side effects. Further, because the antibodies are parenterally administered in treatment of cancer, there normally would be no issues of their ability to cross the mucosa, and the like.

In view of the above remarks and amendments to the claims, the Examiner is requested, respectfully, to reconsider and remove this rejection.

2. Written Description

Claims 12-14 and 16 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement.

According to the Examiner, Applicant has not sufficiently described al of the possible members of the genus of "immunosuppressive signal inhibitors of PD-1." Rather, the Examiner asserts that Applicant has only disclosed a single example of a PD-1 signaling inhibitor, namely an anti PD-1 antibody. The Examiner cites Huang (Pharmacology and Therapeutics, 2000, 86: 201-215) as evidence that developing small molecule regulators of protein function requires long periods of trial and error testing.

This rejection is overcome by amending the claims to recite that the inhibitor is an anti-PD-1 antibody.

F. Claim Rejections - Under 35 USC 102(e)

Claims 12-14 and 16 are rejected under 35 USC 102(e) as being anticipated by Wood et al. (US Patent No. 6,808,710).

According to the Examiner, Wood et al. teach methods of cancer treatment, wherein an immune response against a tumor specific antigen is induced (i.e. potentiated) by administering an agent that inhibits the inhibitory (i.e. immunosuppressive) activity of PD-1 (e.g. columns 54 - 56, more specifically columns 55-56, bridging paragraph), wherein the agent may be an anti-PD-1 antibody (e.g. column 48 lines 52 58). The Examiner admits that Wood et al. do not specifically state that their method suppresses cancer metastasis; however, the Examiner contends that one of skill in the art would immediately recognize that a method that treats cancer

by inducing an immune response against tumor antigens inherently induces an immune response against metastasizing cells, and therefore suppresses metastasis.

Therefore, the Examiner concludes that the reference teachings anticipate the instant claimed invention.

For the following reasons, the rejection is traversed and/or overcome.

The claims have been amended to recite that the "immunosuppressive signal inhibitor of PD-1, PD-LI or PD-L2" is "completely human PD-1 antibodies" and to recite that administration is to a patient with cancer in which PD-L1 or PD-L2 is over-expressed.

Wood et al. do not teach completely human PD-1 antibodies.

More specifically, Wood et al. states at column 14, lines 58-62, that the humanized PD-1 antibodies include antibodies made by a non-human cell having variable and constant regions, which have been altered to more closely resemble antibodies that would be made by a human cell. Wood et al. states at column 36, lines 5-7, that humanized antibodies can be made according to standard protocols such as those disclosed in US 5,565,332, which is a patent directed to production of chimeric antibodies. Therefore, the humanized PD-1 antibodies of Wood et al. undoubtedly mean chimeric antibodies, whereas the completely human PD-1 antibodies of the present application mean PD-1 antibodies derived from only human immunoglobulin genes.

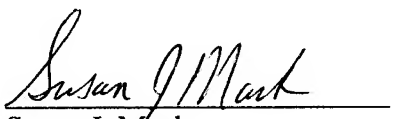
Furthermore, Wood et al. do not teach "administering antibodies to a patient with cancer in which PD-L1 or PD-L2 is over-expressed."

Accordingly, Wood et al. do not teach each and every element of the claimed invention. Therefore Wood et al. cannot anticipate the present invention, and the rejection should be removed.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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